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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,804	06/07/2007	Thomas Bouquin	0279us310	6931

30560 7590 05/24/2011

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
05/24/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/587,804	BOUQUIN, THOMAS
	Examiner	Art Unit
	TERESA WESSENDORF	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6,15,58,63 and 66-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6,15,58,63 and 66-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/15,3/22/11*.	6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 3-6, 15, 58, 63 and 66-70 are pending and under examination.

Claims 1-2, 7-14, 16-57, 59-62 and 64-65 have been cancelled.

Withdrawn objection/Rejection Specification

In view of the amendments to the claims and applicants' arguments the objection to the specification with respect to the abstract and rejections under the 35 USC 102 over Ciceri and Light are withdrawn.

Claim Rejections - 35 USC § 112

Claims 3-6, 15, 58, 63 and 66-70, as amended and added, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record and reiterated below.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification provides the definition for each of the component employed in the method. For example, "nucleic acid sequence", "polynucleotide sequence" or "polynucleotide" is defined as a nucleic acid (which is a polymer of nucleotides (A,C,T,U,G, etc.) or naturally occurring or representing a nucleic acid, depending on context. Either the given nucleic acid sequence or the complementary nucleic acid sequence can be determined from any specified polynucleotide sequence. Similarly, an "amino acid sequence" is defined as a polymer of amino acids (a protein, polypeptide, etc.) or a character string representing an amino acid polymer, depending on context. The "population of cells" in the context of the present invention may be any population of any type of cell, in particular eukaryotic cells. The population may comprise cells expressing a library of polypeptides, e.g. a naive antibody library or a library of polypeptide variants where the aim is to identify antibodies or polypeptide variants

in the library having a desired binding affinity, or it may comprise a collection of cell clones where the aim is to e.g. identify clones having a high and uniform expression level of a polypeptide of interest. For cell populations that express a library of polypeptides, these may for example be a naive antibody library, an antibody library obtained via immunization with a target of interest, or a library of an antibody or non-antibody polypeptide of interest. (Specification e.g., page 10, line 4 up to page 22, line 10). The definitions envision huge compounds of the method. The specification envisions at e.g., pages 45-47; a method of screening and selecting mammalian cell for monoclonal antibody (mab) for FACS-based enrichment. A full-length human antibody library is constructed. Two independent retroviral vectors exhibiting different antibiotic resistance markers are constructed to produce the mAB light chain library (LC lib) and heavy chain library (HC lib), as shown in Figures 19 and 20. As gleaned from the above description, the disclosure describes only mab library in a retroviral vector with the stop codon that binds to antigen. Therefore, the skilled artisan cannot envision all the contemplated substance possibilities recited in the instant claim method as defined by the immense compounds provided in the definitions above. Even if one accepts that the example described in the specification meets the claim

limitations of the rejected claims with regard to structure and function, the example is only representative of a single encoded polypeptide, mab that binds specifically to an antigen using retroviral. The results are not necessarily predictive of other cells, polypeptide variants, reporter peptide and termination suppression agent use in the method. Firstly, because the stop codons are not necessarily universal, with consideration variation amongst organelles (e.g., mitochondria and chloroplasts), viruses (e.g., single strand viruses), and protozoa (e.g., ciliated protozoa) as to whether the codons UAG, UAA, and UGA signal translation termination or encode amino acids. Even though a single release factor most probably recognizes all of the stop codons in eukaryotes, it appears that all of the stop codons are not suppressed in a similar matter. For example, in the yeast Saccharomyces pombe, nonsense suppression has to be strictly codon specific. In another example, significant differences were found in the degree of suppression amongst three UAG codons and two UAA codons in different mRNA contexts in Escherichia coli and in human 293 cells, although data suggested that the context effects of nonsense suppression operated differently in E. coli and human cells. Since unconventional base interactions and/or codon context effects have been implicated in nonsense suppression, it

is conceivable that compounds involved in nonsense suppression of one stop codon may not necessarily be involved in nonsense suppression of another stop codon. In other words, compounds involved in suppressing UAG codons may not necessarily be involved in suppressing UGA codons. (Welch et al, USP 72914610). Given the very large genus of cells, polypeptide variants, stop codons and termination suppression agent encompassed by the method claims, and given the limited description provided by the prior art and specification with regard to the regulation of stop codon read-through sequences that provide structures to support detectable binding, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus. There is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision the various claim components that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention.

Adequate written description requires more than a mere statement that it is part of the invention. See Fiefs v. Revel, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of

Patent Application Under the 35 U.S.C.II2, ¶1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Response to Arguments

Applicants state that the claims have been amended to specify that the cells are eukaryotic cells, the termination suppression agent is an aminoglycoside antibiotic and that FACS is used to carryout the selection step in c). Applicants submit that the level of skill and knowledge in the art is such that those skills in the art would know from the description provided by applicant that polynucleotide encoding any number of polypeptide variants could be used in the method. The degree of predictability within the claimed genus is high because the skill person would expect expression of

the polypeptide variant by following the steps in the specification. With regards to the Examiner's objection to the terms stop codons, Applicants believe that no issue is raised by reference to this genus because it is described in the specification and is also well known in the art.

In reply, the amendments to the claims do not obviate the written description requirement of the claim gene method employing any kind of eukaryotic cells, aminoglycoside antibiotic as the suppression agent and selection by FACS. Applicants have not proffered any evidence that skilled in the art given the description of a single species can correlate the species to any type of polynucleotide variants using the steps for the single species. The results and/or conditions employ for the single species are not necessarily predictive of other cells, polypeptide variants, reporter peptide and at least one stop codon use in method. As stated above, firstly, because the stop codons are not necessarily universal, with considerable variation amongst organelles (e.g., mitochondria and chloroplasts), viruses (e.g., single strand viruses), and protozoa (e.g., ciliated protozoa) as to whether the codons UAG, UAA, and UGA signal translation termination or encode amino acids. Even though a single release factor most probably recognizes all of the stop codons in eukaryotes, it appears that all of the stop codons are not suppressed a similar

matter. For example, in the yeast Saccharomyces pombe, nonsense suppression has to be strictly codon specific. In another example, significant differences were found the degree of suppression amongst three UAG codons and two UAA codons in different mRNA contexts Escherichia coli and in human 293 cells, though data suggested that the context effects of nonsense suppression operated differently in E. coli and human cells. Since unconventional base interactions *and/or* codon context effects have been implicated in nonsense suppression, it is conceivable that compounds involved in nonsense suppression of one stop codon may not necessarily be involved in nonsense suppression of another stop codon. In other words, compounds involved in suppressing UAG codons may not necessarily be involved suppressing UGA codons. (Welch et al, USP 72914610). Furthermore, as well known in the art, insertion of a library of polypeptide variants in a host can be toxic to a host cell hence prohibiting expression or that some cells may not be represented during expression.

A written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials". University of California v.Eli Lilly, 43 USPQ 2d 1398, 1405(1997).

Applicants refer to the Written Description Training Materials published by the USPTO on March 25, 2008 as to the guidance for evaluating compliance to the written description requirement. Example 16 is cited in particular which claims a generic method wherein one nucleic acid is reacted with the known compound X.

In reply, the fact situation in Example 16 is different in the instant claim generic method wherein a library of polypeptide variants (not a single polypeptide) are claimed of no defined structures/formula or unnamed library of polypeptides cultivated with any type of a collection of eukaryotic cells which expression can be stop by any kind or number stop of codon and sorted by FACS. As evident from the cited Welch et al reference there are numerous factors to enable one to screen/select from any library of peptide expressed by a library polynucleotide from any eukaryotic cells. Welch teaches that even the use of single parameter, stop codon affects expression of a polypeptide from a host cell. The level skill in the art is high because the unpredictability in this art is equally high too. Applicants argue that numerous examples of a first polynucleotide encoding a polypeptide variant and at least one stop codon (e.g., Example 2 (UAA/UGA and Protein C), Example 4 (UAA and Factor VII); Example 5 (UGA and Interferon *a)*.

In reply, though understanding the claim language may be aided by explanations contained in written description, it is important not to import into a claim limitations that are not part of claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment. Superguide Corp. v. DirecTV Enterprises, Inc., 358 F.3d 870, 875, 69 US d 1865, 1868 (Fed. r. 2004). MPEP 2111.01(11). There is no indication the specification that the description of the 3 species is representative of the huge scope of the claim method that employs unnamed or undefined structural compounds. The written description requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). Further, written description requirement promotes the progress of the useful arts by ensuring that patentees adequately describe their inventions in their patent specifications in exchange for the right to exclude others from practicing the invention for the duration of the patent's term. To satisfy the written description requirement, a

patent specification must describe the claimed invention in sufficient detail that one skilled the art can reasonably conclude that the inventor had possession the claim invention. See, e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. See MPEP 2163.

Claim Rejections - 35 USC § 112, second paragraph

Claims 3-6, 15, 58, 63 and 66-70, as amended and added, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record as reiterated below.

1. Claim 3, step b) recites the limitation "the presence of a termination suppression agent." There is insufficient antecedent basis for this limitation in the claim.

2. This rejection has the same import to claim 6 "the surface of said cell".

3. Claim 15 recites the limitation "the absence of a termination suppression agent." There is insufficient antecedent basis for this limitation in the claim.

Response to Arguments

While applicants appreciate that certain terms can be unclear whether it is uncertain as to what element a limitation is referring to applicants do not believe that the situation presents itself in the limitations specified in this rejection. Applicants argue that failure to provide explicit antecedent basis for terms does not always render a claim indefinite. A claim is not indefinite if the scope of the claim would be reasonably ascertainable by those skilled in the art. MPEP 2173~05(e), citing Energizer Holding Inc. v. Int'l Trade Comm'n, 77 USPQ2d 1625 (Fed. Cir. 2006) and Ex parte Porter, 25 USPQ2d 144,1145 (Bd. Pat. App. & Inter. I992). In this case, Applicants submit that the meaning of the terms "presence"" and "absence" are clear. With respect to the limitation of "the surface of said cell", it is submitted that antecedent basis is provided in the recitation of "a plurality of eukaryotic cells "in step a}. The "surface" is an inherent component of "cells" and does not require an antecedent recitation to "a surface of said at least

one cell". MPEP 2173(d)5(e) citing Bose Corp v. JBL, Inc. 61, USPQ2d 1216, 1218-1219 (Fed. Cir. 2001).

In reply, the preceding step a) does not recite that a termination suppression agent is required for expression of the polypeptide variant rather only stop codon. Thus, this phrase is indefinite in reference to "the termination suppression agent" as not one of the preceding steps recited for the "presence of termination suppression agent". It is suggested to replace "the" with -a— to obviate this rejection.

Furthermore, "the absence" is not clear given that the base claim recites the presence of a termination suppression agent and FACS analysis using a cell membrane anchoring peptide and not in soluble form. There is nothing in the base claim to ascertain that in the absence of termination agent the peptide becomes soluble (e.g., without the anchoring membrane).

With respect to "the surface" as being inherent to the cells however, the base claim does not recite display of the fusion protein at "the surface" of said cell for FACS selection.

Again, it is suggested that "the' be changed to -a--.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 102

Claims 3-6, 15, 58, 63 and 66-70, as amended and added, are rejected under 35 U.S.C. 102(e) as being anticipated by Hoogenboom et al (USP 7919257).

For claims 3-6, 15, 58, 63 and 66-69; Hoogenboom discloses at e.g., col. 4, line 20+; a method for selecting combinations of proteinaceous molecules having specific affinity for at least two target epitopes, comprising contacting a collection with the two target epitopes and selecting combinations showing the specific affinity.

Hoogenboom discloses at e.g., FIG. 9; screening antibody mixtures produced by the same host cell for optimal bio-activity. Mixtures are made by transfecting heavy chain genes encoding the antibodies of interest together with optimally paired light chain, followed by cloning of cell lines, selecting stably producing cell lines, and eventually screening the resulting antibody mixtures for optimal bio-activity. An element useful for control of the production is placing expression of different variable regions under control of different elements such as promoters, terminators, anti-repressors, repressors, and the like. These control elements may be inducible or repressible. Thus, the production of variable regions can be

regulated, thus optimizing pairing conditions as desired. An expression system for carrying out a method comprises nucleic acids encoding variable regions together with all elements required for gene expression and pairing, preferably such an expression system comprises at least one recombinant cell, such as a yeast cell, a fungal cell, an insect cell, a plant cell or another eukaryotic cell, in particular, a mammalian cell, more in particular, a human **cell**. A collection of expression systems comprises a variety of combinations of different specificities typically as a library for use in selecting desired combinations of variable regions.

For claim 66, Hoogenboom discloses at e.g., FIG. 24: histidine tag (six Histidines); other C-terminal-based tags are also indicated. A stop codon (indicated with *) in the CDR2 region. By site-directed mutagenesis, the CDR2 is diversified using an oligonucleotide that simultaneously removes the stop codon as well as introduces diversity at three positions of the CDR2. Hoogenboom discloses at e.g. col. 13, line 15+; antibodies or antibody fragments can also be isolated using display-based antibody library technology, wherein antibody fragments are selected by exposing a library of such antibodies displayed on the surface of phage, yeast or other host cell, to

the antigen of interest, and isolating those antibody fragments which bind to the antigen preparation. A display library is a collection of entities; each entity includes an accessible polypeptide component and a recoverable component that encodes or identifies the peptide component. Another display format of the library **is a cell**-display library. Proteins are displayed on the surface of a cell, e.g., a eukaryotic or prokaryotic cell. Cited selection and screening technologies of recombinant antibodies and their fragments are well established in the field. Antigen-specific polypeptides can be identified from display **libraries** by direct screening of the library, or can be first selected on antigen to increase the percentage of antigen-reactive clones. The selection process may be accomplished by a variety of techniques well known in the art, by using, inter alia, **cell** sorting, especially fluorescence-activated **cell** sorting (FACS). Hoogenboom discloses that the methods and compositions are also suitable for automated screening of diversity libraries for finding clones with likely pairing-compatible variable regions. For example, a display library of Fabs or scFvs can be screened for members that bind to a target molecule. The library can be screened directly or first selected on antigen once or several times. Binders from a first round of screening can be amplified and rescreened, one or more times.

Binders from the second or subsequent rounds are individually isolated, e.g., in a multi-well plate. Each individual binder can then be assayed for binding to the target molecule, e.g., using ELISA, a homogenous binding assay, or a protein array. These assays of individual clones can be automated using robotics. Sequences of the selected clones can be determined using robots.

For claims 3 and 66-67, Hoogemboom discloses e.g., Example 17; a stop codon and epitope tag.

For claim 15, Hoogenbomm discloses at e.g., Example 19; the soluble fusion protein VEGF-R2 fused to alkaline phosphatase (VEGF-R2-AP) is expressed in stably-transfected NIH 3T3 cells and purified from cell culture supernatant by affinity chromatography.

For claim 63, Hoogenboom disclose at e.g., col. 32, line 63 up to col. 33, line 35+; G418, hygromycin on a host cell into which the vector has been introduced.

The claim positioning of the first polynucleotide and second polynucleotides would be inherent to the process of Hoogenboom given the same process steps, as claim and the use of specific components in the process.

Claim Rejections - 35 USC § 103

Claims 3-6, 15, 58, 63 and 66-70, as amended and added, are rejected under 35 U.S.C. 103(a) as being unpatentable over Ciceri(USP 20070105093) or Light et al (U.S. Patent 5,770,356) in view Manuvakhova et al (RNA, 1000, 1044-55) and Sabbadini et al (7183105)(if necessary, together with Hoogenboom which teaches the functional equivalence of eukaryotic cells and phage).

Ciceri et al discloses at e.g., the following claims; claim 1, a method of producing a fusion protein displayed on the surface of a phage in an expression system comprising a phage-derived nucleic acid construct containing a sequence encoding said fusion protein, said construct comprising, in a 5' to 3' orientation, a promoter and/or regulatory region operably linked to a sequence encoding a fusion protein further comprising a phage surface protein operably linked to a sequence comprising a termination codon operably linked to a sequence encoding a heterologous polypeptide; and a suppressor construct comprising, in a 5' to 3' orientation, an inducible promoter and/or regulatory region operably linked to a sequence encoding a suppressor tRNA capable of recognizing said termination codon of said phage-derived nucleic acid construct; wherein said method

comprises the steps of: (i) expressing the phage surface protein at the phage propagation step by not inducing said suppressor tRNA and (ii) expressing the phage-displayed fusion protein at the phage display step by inducing the expression of said suppressor tRNA.

2. The method of claim 1 wherein said expression system is in an E. coli cell.

14. The method of claim 1 wherein said suppressor tRNA is tRNA.Ala or tRNA.Glu.

15. The method of claim 1 wherein said suppressor tRNA is tRNA.Ala.

16. A method of producing a fusion protein displayed on the surface of a phage comprising the steps of: (i) propagating said phage in a first expression system wherein said phage is a nucleic acid construct containing a sequence encoding said fusion protein, said construct comprising, in a 5' to 3' orientation, a promoter and/or regulatory region operably linked to a sequence encoding a fusion protein further comprising phage surface protein operably linked to a sequence comprising a termination codon operably linked to a sequence encoding a heterologous polypeptide; and (ii) expressing said fusion protein by inducing the expression of suppressor tRNA in a second expression system comprising said nucleic acid construct in step (i) and a suppressor construct comprising, in a 5' to 3' orientation, an inducible promoter and/or regulatory region operably linked to a sequence encoding said suppressor tRNA capable of recognizing said termination codon of said nucleic acid construct.

17. The method of claim 16 wherein said first expression system further comprises a second construct comprising, in a 5' to 3' orientation, an inducible promoter operably linked to a sequence encoding a phage surface protein, wherein expression of said phage surface protein aids the propagation of said phage.

18. The method of claim 18 wherein said expression system is in an E. coli cell.

Ciceri at e.g., paragraph [0038] discloses the phage derived and suppressor constructs of the invention are preferably selectable based upon different markers present on each construct.

Light

For claims 3, 6 and 15; Light discloses throughout the patent e.g., at col. 17, lines 30 up to col. 38, line 35 a method of expressing both anchored and non-anchored soluble heterologous polypeptides in a single vector in which nucleotide sequences are present for encoding: a) a suppressor tRNA gene capable of expressing a suppressor tRNA molecule; and b) an expression cassette for expressing a first and second heterologous polypeptide subunit. The cassette is designed to produce both subunits, one anchored to a phage membrane coat protein and the other not anchored, i.e., soluble, through the regulation of a nonsense chain termination codon and a tRNA suppressor gene. Exemplary expression cassettes for use with a tRNA suppressor gene are present in expression vectors, the latter of which are those that provide for the expression of

bacterial alkaline in either the non-anchored soluble form such as pPhoC as described in Example 8, or in the anchored form such as pPho8, pPhoL8 and pPhoL8B as described in Example 5. Light discloses the epitope tag at e., col. 39, line 65.

Ciceri or Light does not teach the suppressor agent as aminoglycoside antibiotic, e.g., G-418 species, the cells are screened by FACS machine and the cell membrane is GPI as the cell membrane anchoring peptide. However, Manuvakhova et al teaches at e.g., page 1044, the abstract that aminoglycoside antibiotics can reduce the efficiency of translation termination. Manuvakhova further teaches at page 1045, col. 2 that G418 can suppress premature stop mutations in a gene. Sabbadini disclose at e.g., col. 127, line 29 up to col. 128, line 5, FACS analysis of isolated cells. Sabbadini further discloses at e.g., col. 165, lines 26-50 the incorporation of GPI anchors and other membrane-targeting elements into the amino-or carboxy-terminus of a fusion protein can direct the chimeric molecule to the cell surface. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use FACS to screen cells as this is the conventional way of screening or sorting out cells from a pool or library as taught by Sabbadini. One would have a

reasonable expectation of success since FACS has been used to screen cells in a population as achieved by Sabbadini. Furthermore to use aminoglycoside antibiotic as the suppressor agent as taught by Manuvakhova in the method of Ciceri would be expected since amino glycoside has been tested for different cells and found to suppress termination cordons. Likewise, it would have been obvious to use GPI in the method of Light or Ciceri as taught by Sabatini reasonably expecting that since GPI is a known membrane anchoring peptide would provide the anchor for the peptide to the cells. Accordingly, the combined teachings of the prior art renders the claim prima facie obvious to one having ordinary skill in the art at the time of filing. Furthermore, it would have been obvious to one having ordinary skill in the art to use the select the salt e.g., butyrate, as claim to optimize the expression of peptides and/or results which would depend upon the specific components use in the method.

Response to Arguments

Applicants argue that there is no disclosure or suggestion in the Light et al patent or Ciceri publication to perform the claimed method which requires, inter alia, the cultivation: of eukaryotic calls in the presence of an aminoglycoside antibiotic and FACS. The Ciceri et at. reference further teaches away from

claim element a) which requires the cell membrane anchoring peptide to be downstream of the at least one stop codon. In contrast, Ciceri et al. describe the advantage to be the fact that the coat protein can be expressed without expression of the heterologous protein not vice-versa. Neither reference provides any motivation to deviate from the use of suppressor tRNA genes or phage display.

Addition of the Manuvakhova et al, Sabbadini et al references does render the claimed invention obvious.

No where does the Manuvkhova et al. reference describe or suggest the use of aminoglycoside in a method for screening or selecting a cell expressing a polypeptide with a desired binding affinity to a ligand, as claimed. Applicants however admit that the references, does shed some light as to the motivation for the studies. Manuvakhova et al state that a pharmacological approach aimed at suppressing premature stop mutations may be applicable to common genetic diseases such as cystic fibrosis and muscular dystrophy. Page 1045, left column. The Sabbadini et al reference is being cited for its disclosure of FACS analysis of isolated cells and the incorporation of GPI and other membrane targeting elements in a fusion protein to direct the chimeric molecule to the ceil surface. None of the cited references provide any motivation for completely substituting

the phage display system described in Light et al. and Ciceri et al references with a call-based screening method which utilizes an aminoglycoside antibiotic.

In reply, one cannot show non-obviousness by attacking the references individually where the rejection is based on a combination of references. In re Young, 159 USPQ 725 (CCPA 1968). Thus, while Ciceri or Light does not teach eukaryotic cells however, Sabbadini et al teaches said cells (Hoogenboom teaches the functional equivalence of phage and eukaryotic cells in expressing polypeptides). Furthermore, as applicants admitted above Manuvakhova and Sabbadini provides the motivation to use aminoglycoside antibiotic and FACS. The combined teachings of the prior art renders the claim prima facie obvious.

> When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007).

Similarly, herein the claimed invention is no more than a predictable use of the known elements in the known method steps.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS**

ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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